INFORMATION

Metopon Hydrochloride*†

In 1929 with the funds provided by the Rockefeller Foundation the National Research Council, through its Committee on Drug Addiction, undertook a coordinated program to study drug addiction and search for a non-addicting analgesic comparable to morphine. The principal participating organizations were the Universities of Virginia and Michigan, the United States Public Health Service, the Treasury Department's Bureau of Narcotics, and the Health Department of the State of Massachusetts, which brought together chemical, pharmacological and clinical facilities for the purposes of the study. Metopon is one of the many compounds made and studied in this coordinated effort.

Chemically Metopon is a morphine derivative; pharmacologically it is qualitatively like morphine even to the properties of tolerance and addiction liability. Chemically Metopon differs from morphine in three particulars: one double bond of the phenanthrene nucleus has been reduced by hydrogenation; the alcoholic hydroxyl has been replaced by oxygen; and a new substituent, a methyl group, has been attached to the phenanthrene nucleus. Studies made thus far indicate that pharmacologically Metopon differs from morphine quantitatively in all of its important actions: its analgesic effectiveness is at least double and its duration of action is about equal to that of morphine; it is nearly devoid of emetic action; tolerance to it appears to develop more slowly and to disappear more quickly and physical dependence builds up more slowly than with morphine; therapeutic analgesic doses produce little or no respiratory depression and much less mental dullness than does morphine; and it is relatively highly effective by oral administration.

In addition to animal experiments these differences have been established by extensive employment of the drug in two types of patients—individuals addicted to morphine, and others (terminal malignancies) needing prolonged pain relief but without previous opiate experience. In morphine addicts, Metopon appears only partially to prevent the impending signs of physical and psychical dependence. In terminal malignancy, administered orally, it gives adequate pain relief, with very little mental dulling, without nausea or vomiting and with slow development of tolerance and dependence.

The high analgesic effectiveness of oral doses (with the elimination of the disadvantage to the patient of hypodermic injection), the absence of nausea and vomiting even in patients who vomit with morphine or other derivatives, the absence of mental dullness and the slow development of tolerance and dependence place Metopon in a class by itself for the treatment of the chronic suffering of malignancies, and it is for that purpose exclusively that it is being manufactured and marketed.

Metopon will be available *only* in capsule form *for oral administration.* The capsules will be put up in bottles of 100 and each capsule will contain 3.0 mgm. of Metopon hydrochloride. They can be obtained by physicians only from Sharp & Dohme or Parke, Davis & Co., on a regular official Narcotic Order Form, which must be accompanied by a signed statement supplying information as to the number of patients to be treated and the diagnosis on each. The drug will be distributed for *no other purpose* than oral administration for chronic pain relief in cancer cases.

The dose of Metopon hydrochloride is 6.0 to 9.0 mgm. (2 or 3 capsules), to be *repeated only on recurrence of pain,* avoiding regular by-the-clock administration. As with morphine, it is most desirable to keep the dose at the lowest level compatible with adequate pain relief. Therefore, administration should be started with two capsules per dose, increasing to three only if the analgesic effect is insufficient.

Tolerance to any narcotic drug develops more rapidly with excessive dosage and under regular by-the-clock administration. Also, as a rule, the pain of cancer varies widely in intensity from time to time. Pain, therefore, should be the only guide to time of administration and dosage level. Tolerance to Metopon hydrochloride develops slowly. It can be delayed or interrupted entirely by withholding the drug occasionally for 12 hours or for as much of that period as the incidence of pain will permit.

To each physician will be sent a record card for each patient to whom Metopon hydrochloride is to be administered. He will be requested to fill out these cards and return them in the addressed return envelope. He must furnish this record of his patient and his use of Metopon hydrochloride if he wishes to repeat his order for the drug. The principal object of this detailed report is to check the satisfactoriness of Metopon hydrochloride administration in general practice. The physician's cooperation in making it as complete as possible is earnestly solicited.

The limited use of Metopon hydrochloride as described above has been recommended by the Drug Addiction Committee of the National Research Council and the Committee with the cooperation of the American Cancer Society, will supervise the distribution of the drug. The Committee is composed of Wm.

* Methyldihydromorphinone hydrochloride.

† This article on Metopon Hydrochloride was prepared by the Committee on Drug Addiction, Division of Medical Sciences of the National Research Council.

Charles White, Chairman, Washington, D. C.; H. J. Anslinger, Commissioner of Narcotics, United States Treasury Department, Washington, D. C.; Lyndon F. Small, National Institute of Health, Washington, D. C.; and Nathan B. Eddy, National Institute of Health, Washington, D. C. Queries and comments on Metopon may be directed to Dr. Eddy, who will answer them for the Committee.

U.S. Bond Purchase Plan For Doctors Offered

The nation's banks, by arrangement with the United States Treasury Department, are offering to physicians and other self-employed individuals a systematic savings investment plan under which regular monthly deductions may be made from their checking accounts for the purchase of United States Savings Bonds.

Designed to meet the need of physicians for an orderly investment system requiring a minimum of supervision, the plan, which already is in operation, provides that a depositor who wishes to buy a bond each month has only to sign a card authorizing his bank to deduct from his checking account the purchase price of the bond in whatever denomination he chooses. Each month the bank delivers the bond to the customer, whose periodic bank statements show the deductions for payments.

The following table has been prepared by the Treasury Department to show the aggregate of savings and accumulated interest under the "Bond-A-Month Plan":

If you invest each month under the Bond-a-Month Plan	In five years you will have	In ten years you will have
$ 37.50	$ 2,319.00	$ 4,998.00
75.00	4,638.00	9,996.00
150.00	9,276.00	19,992.00
300.00	18,522.00	39,984.00

Letters to the Editor . . .

ASCORBIC ACID WITHHOLDING THERAPY

The possibility of controlling malarial infection by reduced intake of vitamin C (ascorbic acid) is suggested by McKee[3] and his co-workers of the Department of Comparative Pathology, Harvard Medical School.

During the course of malarial studies with monkeys, inoculated with *P. knowlesi*, the Harvard investigators inoculated seven monkeys with spontaneous vitamin C deficiency and an additional group of monkeys rendered deficient by previous feeding on Shaw's[4] ascorbic acid free synthetic diet. In control animals on normal diets containing adequate amounts of ascorbic acid there was usually a rapid increase in the number of parasites in the circulating blood, with death within six to seven days. In the ascorbic acid deficient animals there was only a slow rise in the percentage of parasites with a gradual spontaneous control of the infection. Intramuscular injection of 80-100 mg. of ascorbic acid into these animals was followed by a rapid increase in the number of malarial parasites, with death within two to six days.

The tests indicate that in monkeys a relatively high ascorbic acid titer of the blood stream is necessary for the rapid multiplication of the malarial plasmodium, low titers serving as an inhibiting mechanism. Whether or not this inhibiting action of vitamin C deficiency is due to a direct action on the parasites or to an indirect one through the animal host, is not yet determined. McKee is inclined to attribute it to an indirect action, since attempts thus far to demonstrate the need of ascorbic acid for the *in vitro* growth and multiplication of *P. knowlesi* have been inconclusive.

Studies by Marin,[2] Horvitt[1] and others suggest that the interrelationship between malarial parasites and ascorbic acid is the same in humans and monkeys. If so, ascorbic acid withdrawing therapy may be of future clinical interest.

REFERENCES

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